HFA-305

NOV 29 1999

FREEDOM OF INFORMATION SUMMARY
FOR
REVALOR®200 (TRENBOLONE ACETATE AND ESTRADIOL)

1. GENERAL INFORMATION

NADA Number:	140-992
Sponsor:	Hoechst Roussel Vet 30 Independence Blvd. P.O. Box 4915 Warren, NJ 07059
Generic Names:	Trenbolone Acetate and Estradiol
Trade Name:	REVALOR®-200
Marketing Status:	Over the counter (OTC)
Effect of Supplement:	Provides for the administration of REVALOR®-200 in steers fed in confinement for slaughter for increased rate of weight gain and improved feed efficiency.

2. INDICATIONS FOR USE

For increased rate of weight gain and improved feed efficiency in steers fed in confinement for slaughter.

3. DOSAGE FORM(S), ROUTE(S) OF ADMINISTRATION AND RECOMMENDED DOSAGE

Dosage Form:	Implantation
Route of Administration:	Subcutaneous implantation on the posterior aspect of the ear.
Recommended Dosage:	One implant containing 200 mg trenbolone acetate and 20 mg estradiol. Each implant is made up of ten pellets with each pellet containing 20 mg trenbolone acetate and 2 mg estradiol.

4. EFFECTIVENESS

The supplemental new animal drug application for REVALOR®-200 contains data from adequate and well-controlled studies demonstrating the effectiveness of the new animal drug for the indications for use and dosage as given in Sections 2 and 3 above.

NADA 140-992

Pivotal Studies:

The pivotal studies are dose titration studies in which the parameters measured are the same parameters as are measured in field investigations. Four dose titration studies were conducted using a uniform protocol so that the results of the studies could be pooled and summarized. The studies were conducted in the major beef producing areas of the United States.

Name and Address of Investigators:

Dr. Rodney Preston
Texas Tech University
Lubbock, Texas

Dr. Daryl Meyer
Lucerne Enterprises
Fremont, Nebraska

Dr. E.G. Johnson
Johnson Research
Parma, Idaho

Dr. Mary Wray
Horton Feedlot and Research Center
Wellington, Colorado

The purpose of the studies was to evaluate the dose response for trenbolone acetate (TBA) and estradiol (E) on average daily weight gain and feed efficiency in feedlot steers. The test animals (1776 head) were crossbred animals of European and Exotic breeds. For each study 336 to 480 steers were blocked by weight and randomly assigned within block to one of six treatments (8 replicates/treatment). The treatments consisted of Control (no implant), 30 mg E, 300 mg TBA, 10 mg E/100 mg TBA, 20 mg E/200 mg TBA, and 30 mg E/300 mg TBA. The steers weighed between 785 lbs. and 942 lbs. when the studies were initiated. The duration of the studies ranged between 105 to 133 days.

Each steer was administered TBA and E via subcutaneous implantation on the backside of the mid-ear. The steers were administered the implant once at the initiation of each study. After the cattle were implanted they were placed in the feedlot pens for the duration of the study.

Average daily gain (ADG) and feed efficiency (FE) data are summarized in Tables 1 and 2, respectively, for each of the four dose titration studies.

A randomized complete block design was used for all four studies and the data were pooled by analysis of variance to determine the significance of the effect of TBA/E implants on ADG and FE. There was a significant ($P<.01$) linear and quadratic response in ADG and FE to increasing levels of the combination product with the maximum response seen at the 200 mg TBA/20 mg E dose. The 200 mg TBA/20 mg E treatment also was shown to be

significantly (P<.05) better than 300 mg TBA alone and 30 mg E alone. These data are sufficient to support the claims and dosage as provided in Sections 2 and 3.

TABLE 1

SUMMARY OF RESULTS FOR AVERAGE DAILY GAIN (lbs/h/d)

Study Site	Treatment Group[1]					
	Control	30 mg E	300 mg TBA	100mg TBA 10 mg E	200mg TBA 20 mg E	300mg TBA 30mg E
Texas	2.72[a]	2.93[a]	2.83[a]	3.21[b]	3.47[c]	3.48[c]
Nebraska	3.23[a]	3.52[b]	3.54[b]	3.76[c]	3.80[c]	4.03[d]
Idaho	3.61[a]	3.96[b]	3.72[a]	4.20[c]	4.41[d]	4.24[c,d]
Colorado	3.84[a]	4.41[c]	4.04[b]	4.53[c]	4.87[d]	5.00[d]
All Sites	3.35[a]	3.71[c]	3.53[b]	3.93[d]	4.14[e]	4.19[e]

[1]SAS PROC MIXED used to generate statistics, least squares treatment means
[a,b,c,d,e] Means in same row with different superscripts differ significantly at P<0.05

TABLE 2

SUMMARY OF RESULTS FOR AVERAGE FEED EFFICIENCY (DMI/ADG)

Study Site	Treatment Group[1]					
	Control	30mg E	300 mg TBA	100mg TBA 10 mg E	200mg TBA 20 mg E	300mg TBA 30mg E
Texas	6.47[a]	6.35[a]	6.05[b]	5.74[c]	5.50[d]	5.50[d]
Nebraska	7.68[a]	7.07[b]	6.81[c]	6.73[b,c]	6.71[b,c]	6.44[c]
Idaho	6.24[a]	6.10[a,b]	6.16[a,b]	5.93[b,c]	5.77[c]	5.94[b,c]
Colorado	6.60[a]	6.28[b]	6.40[a,b]	5.95[c]	5.66[d]	5.55[d]
All Sites	6.59[a]	6.34[b]	6.23[b]	5.90[c]	5.67[d]	5.61[d]

[1]SAS PROC MIXED used to generate statistics, least squares treatment means
[a,b,c,d] Means in same row with different superscripts differ significantly at P<0.05

5. TARGET ANIMAL SAFETY

The supplemental new animal drug application for REVALOR®-200 references the target animal safety studies summarized in the FOI Summary for NADA 140-992 (60 FR 4367, January 23, 1995). The data from those studies demonstrate the safety of the new animal drug for the indications for use and dosage as given in Sections 2 and 3 above.

6. HUMAN SAFETY

A. Toxicity Tests and Safe Concentration

The toxicity studies summarized in the FOI from NADA 138-612 (52 FR 24994 - July 2, 1987) establish the safe concentration for TBA. An acceptable daily intake (ADI) of 0.0004 mg/kg body weight/day has been established for trenbolone (64 FR 18573). Estradiol is regulated under 21 CFR 556.240 on the basis of allowable incremental increases. Residues for estradiol and related esters may not exceed the following increments above the concentrations of estradiol naturally present in the untreated animals; in the uncooked edible tissues of heifers, steers, and calves, 120 parts per trillion (ppt) for muscle, 480 ppt in fat, 360 ppt for kidney, and 240 ppt for liver.

B. Residue Depletion Study

A tissue residue study was conducted to determine the residues of estradiol and the two metabolites of trenbolone acetate (17α-hydroxytrenbolone (17α-TBA) and 17β-hydroxytrenbolone (17β-TBA)). This residue analysis was conducted by Dr. Donald Henricks, Clemson University, Clemson, SC (Study #4667-01-07-95).

Eight (8) steers were treated with 200 mg trenbolone acetate and 20 mg estradiol. There were also four (4) control steers in the study. In the treatment group, four steers were sacrificed 15 days after treatment and the remaining four were sacrificed 30 days after implantation. In the control group, two steers were sacrificed 15 days after treatment and the remaining two were sacrificed 30 days after the treatment group was implanted. Muscle, liver, kidney and fat samples were collected from each animal at the time of sacrifice. After collection, samples were immediately frozen in dry ice and held frozen until they were assayed for estradiol, 17α-TBA and 17β-TBA.

For estradiol levels, the purpose of the study was to determine the residue levels in the treated animals and compare them to the allowable incremental increases permitted under 21 CFR 556.240. The results are shown in Table 3.

Table 3

Estradiol residues in the tissues of Revalor®-200 treated and control steers.

Tissue	Allowable Incremental Increase (ppt)	Estradiol (ppt)			
		15-day Control	15-day Treated	30-day Control	30-day Treated
Muscle	120	-.-*	13.4±2.4	-.-	13.6±3.7
Liver	240	-.-	84.8±23.9	-.-	28.6
Kidney	360	61.2±9.1	60.4±20.7	98.6±15.7	64.9±22.2
Fat	480	-.-	67.1±16.9	-.-	59.4±20.5

* LOQ for estradiol: 5 ppt muscle and fat; 24 ppt liver and kidney

The results of the estradiol assays from the treated and control animals were compared to the allowable incremental increases permitted under 21 CFR 556.240. When the residues of estradiol in the treated animals were compared to the naturally occurring levels in the untreated controls they were found to be much lower than the allowable incremental increases.

For trenbolone acetate residues, the purpose of the study was to determine the residue levels in the treated animals and compare them to the residues incurred with the approved Finaplix® implant (200 mg trenbolone acetate alone). The residues of 17α-TBA and 17β-TBA are reported in Table 4.

The residues of Revalor®-200 treated animals are less at 30 days post-implantation than at 15 days post-implantation. The liver, kidney and fat residues of trenbolone β resulting from the use of Revalor®-200 were less than the liver, kidney and fat residues of trenbolone β resulting from the use of Finaplix®. For muscle, the residues of trenbolone β are higher in Revalor®-200 treated steers than in Finaplix® treated steers and the difference is statistically significant ($P<.05$). However, the total residue equivalents, adjusted for the method, are less than half of the safe concentration for muscle, 80 ppb (using revised consumption values, 59 FR 37499). Liver residues of trenbolone α resulting from the use of Revalor®-200 were less than liver residues of trenbolone α resulting from the use of Finaplix®. Fat residues of trenbolone α at 15 and 30 days withdrawal and muscle residues of trenbolone α at 15 days withdrawal are higher in Revalor®-200-treated steers than in Finaplix®-treated steers. However, the statistical significance of these observed differences cannot be determined since the trenbolone α residues in the Finaplix® study are less than the validated LOQs for the method. The α trenbolone residues in muscle at 30 days withdrawal in the Revalor®-200 study also are less than the LOQ for the method. Kidney residues of trenbolone α in Revalor® 200-treated cattle appear to be higher than kidney residues of trenbolone α in Finaplix®-treated steers, however, the method LOQ for kidney residues in the Finaplix® study was twice the method LOQ for kidney residues in the Revalor® study, *i.e.*, 250 ppt *vs.* 125 ppt, and, as such, the statistical significance of these observed differences also cannot be determined.

Table 4

Residues of 17α-TBA and 17β-TBA in the tissues of Revalor®-200 treated steers and steers treated with 200 mg of trenbolone acetate (TBA) alone (Finaplix®).

Trenbolone 17α (ppt)								
Tissue	**Revalor® 200**				**Finaplix®**			
	15-day Control	**15-day Treated**	**30-day Control**	**30-day Treated**	**15-day Control**	**15-day Treated**	**30-day Control**	**30-day Treated**
Muscle	-.-*†	19.14 (3.25)	-.-	-.-	-.-*§	-.-	-.-	-.-
Liver	-.-	1550 (932)	-.-	802.2 (239.1)	-.-	4023.1 (2415.3)	-.-	1774.8 (470.3)
Kidney	-.-	178.0 (45.2)	-.-	167.2 (23.7)	-.-	-.-	-.-	-.-
Fat	-.-	60.2 (11.7)	-.-	43.9 (11.5)	-.-	-.-	-.-	-.-
Trenbolone 17β (ppt)								
Tissue	**Revalor® 200**				**Finaplix®**			
	15-day Control	**15-day Treated**	**30-day Control**	**30-day Treated**	**15-day Control**	**15-day Treated**	**30-day control**	**30-day Treated**
Muscle	-.-	279.4 (38.5)	-.-	233.8 (47.2)	-.-	211.3 (39.5)	-.-	138.6 (63.1)
Liver	-.-	239.7 (83.0)	-.-	216.1 (30.1)	-.-	761.7 (161.2)	-.-	497.7 (67.8)
Kidney	-.-	175.7 (21.5)	-.-	129.9 (4.9)	-.-	387.4 (35.3)	-.-	337.1 (66.0
Fat	-.-	378.3 (61.6)	-.-	260.2 (81.1)	-.-	846.6 (73.2)	-.-	660.9 (127.4)

* -.- Values are less than the LOQs for the respective tissues.

† LOQs for the Revalor® 200 study: muscle: 15 ppt TBA-α, 30 ppt TBA-β; fat: 30 ppt TBA-α and TBA-β; liver: 125 ppt TBA-α and TBA β; kidney: 125 ppt TBA-α and TBA-β.

§ LOQs for the Finaplix® study: muscle: 15 ppt TBA-α, 30 ppt TBA-β; fat: 30 ppt TBA-α and TBA-β; liver: 125 ppt TBA-α and TBA-β; kidney: 250 ppt TBA-α and TBA-β.

C. Withdrawal period

Residues of estradiol in steers treated with Revalor®-200 are several times less than the allowable incremental increases permitted under 21 CFR 556.240. No statistical conclusions can be drawn for residues of trenbolone α in muscle, kidney or fat since residues in the Finaplix® study are less than the method LOQ. For liver, kidney and fat trenbolone β and for liver trenbolone α, residues in Revalor®-200-treated steers are less than residues in Finaplix®-treated steers. While muscle residues of trenbolone β are higher in Revalor®-200-treated steers than in Finaplix®-treated steers, the method-adjusted total residue equivalents of trenbolone are less than the

muscle safe concentration, 80 ppb. Therefore, the use of Revalor®-200 qualifies for a zero withdrawal.

D. Regulatory Method

Revalor®-200 qualifies for a zero withdrawal and, as such, a regulatory analytical method for residues is not required.

7. AGENCY CONCLUSIONS

Adequate data is established to demonstrate the safe and effective use of Revalor®-200 (ear implant containing 200 mg TBA and 20 mg estradiol) when used in steers fed in confinement for slaughter for increased rate of weight gain and improved feed efficiency.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)), this is a Category II change providing for the use of Revalor®-200 in steers fed in confinement for slaughter. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of these new animal drugs. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

8. LABELING

Facsimile labeling is attached as follows:

1. Cartridge Label – 10 doses
2. Package Insert (Front)
3. Package Insert (Back)
4. Package Label (Box) – 100 doses (Front)
5. Package Label (Box) – 100 doses (Back)
6. Large Container Label – 1000 doses
7. Large Container Label – 4000 doses

Lot Number:

Expiration Date:

Revalor®-200

(trenbolone acetate 200 mg and estradiol 20 mg)

10 Implants for Steers Fed in Confinement for Slaughter

Distributed by: Hoechst Roussel Vet
Clinton, NJ 08809

Revalor®-200

(trenbolone acetate and estradiol)

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

WARNING

Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for Use in Humans. Implant pellets in the ear only. Any other location is in violation of Federal Law. Do not attempt salvage of implanted site for human or animal food.

STORAGE CONDITIONS

Store in a refrigerator (2-8° C; 36-47° F) and protect from sunlight. Use before the expiration date printed on the cartridge.

PACKAGE QUANTITIES

Box of 10 x 10 cartridge implants.

Made in France by:
Hoechst Roussel Vet, S.A.
Distributed by:
Hoechst Roussel Vet, S.A.
30 Independence Blvd.
Warren, NJ 07059

482020-A

Hoechst Roussel Vet

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DESCRIPTION

Revalor®-200 (trenbolone acetate, CAS Registry Number 10161-34-9, and estradiol, CAS Registry Number 50-28-2) is an implant containing 200 mg of trenbolone acetate and 20 mg estradiol. Each implant consists of 10 small yellow pellets. Ten implants are provided in a cartridge.

Manufactured by a non-sterilizing process.

INDICATIONS FOR USE

This product contains trenbolone acetate and estradiol in a slow-release delivery system which increases rate of weight gain and improves feed efficiency in feedlot steers.

NOTE

Studies have demonstrated that the administration of Revalor®-200 can result in decreasing marbling scores when compared to non-implanted steers.

DOSAGE:

Dosage Form:
One implant containing 200 mg trenbolone acetate and 20 mg estradiol is administered to each animal. The 10 pellets which make up the dosage of Revalor®-200 are contained in one division of the multiple dose cartridge. Ten doses are in each cartridge. The cartridge is designed to be used with a special implant gun.

Route of Administration:
The implant is placed under the skin on the posterior aspect of the ear by means of a special implanter available from Hoechst Roussel Vet.

With the animal suitably restrained, the skin on the outer surface of the ear should be cleaned. The implant is then administered by the method shown in the diagram below.

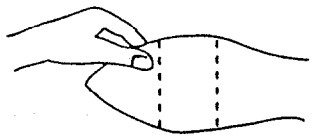


Fig. 1 - Ear of Bovine Ready for Implantation

SITE OF IMPLANTATION

After appropriately restraining the animal to allow access to the ear, cleanse the skin at the implant needle puncture site. It is subcutaneous between the skin and cartilage on the back side of the ear and below the midline of the ear. *The implant must not be placed closer to the head than the edge of the cartilage ring farthest from the head.* The location of insertion of the needle is a point toward the tip of the ear and at least a needle length away from the intended deposition site. Care should be taken to avoid injuring the major blood vessels or cartilage of the ear.

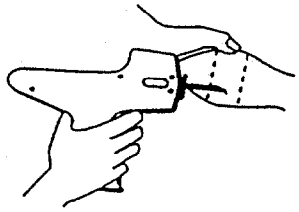


Fig. 2 - Rear View of the Bovine Ear Showing the Site for Insertion of the Implanter Needle.

METHOD OF USE

1. Do not remove the cap of the cartridge containing the implants.
2. Place the cartridge (D) (with the capped end to the front) into slot at the top of the implanter magazine (marked A on the diagram).
3. Gently push the cartridge into the slot until it clicks into place.
4. The implanter is then ready for use.
5. Take the ear of the animal firmly with the free hand (in the manner shown in Fig. 1). Then insert the needle into the subcutaneous tissue at the point indicated (in Fig. 2).
6. After inserting the needle to its full extent, squeeze the trigger (E) gradually. Allow the pellets of the implant to be deposited in a single row.
7. Withdraw the implanter. This will advance the cartridge one groove in the magazine and the next implant is now ready for use.
8. When all the implants have been administered, the cartridge will fall out of the bottom of the magazine and may be replaced by a new one.
9. To change the needle, loosen the needle locking nut (labeled F in Fig. 3) and replace the needle. Tighten the nut finger tight and the implanter is ready for use.

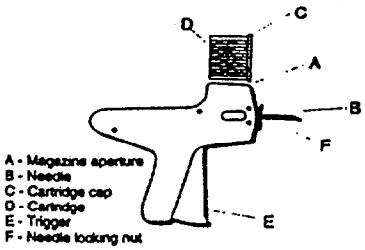
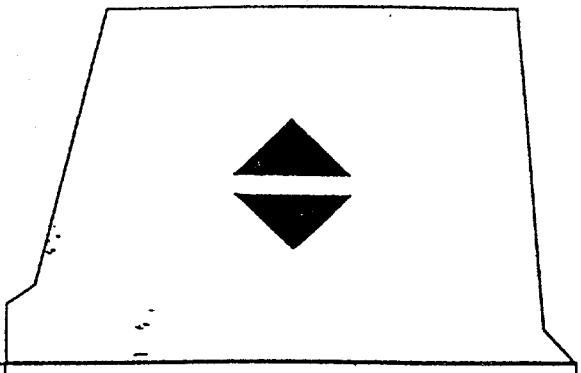


Fig. 3 - Diagram of the Implanter and Cartridge



Revalor-200

(trenbolone acetate and estradiol)

Expiration Date:

Lot Number:

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

Box of 10 x 10 Cartridge Implants

Manufactured by a non-sterilizing process
The name and logo Hoechst are registered trademarks of Hoechst AG.

Hoechst Roussel Vet

Revalor®-200 is a registered trademark of Hoechst Roussel Vet, S.A.

USE DIRECTIONS:
See enclosed package insert.

WARNING:
Not to be used in animals for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for Use in Humans. Implant pellets in the ear only. Any other location is in violation of Federal Law. Do not attempt salvage of implanted site for human or animal food.

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Hoechst Roussel Vet
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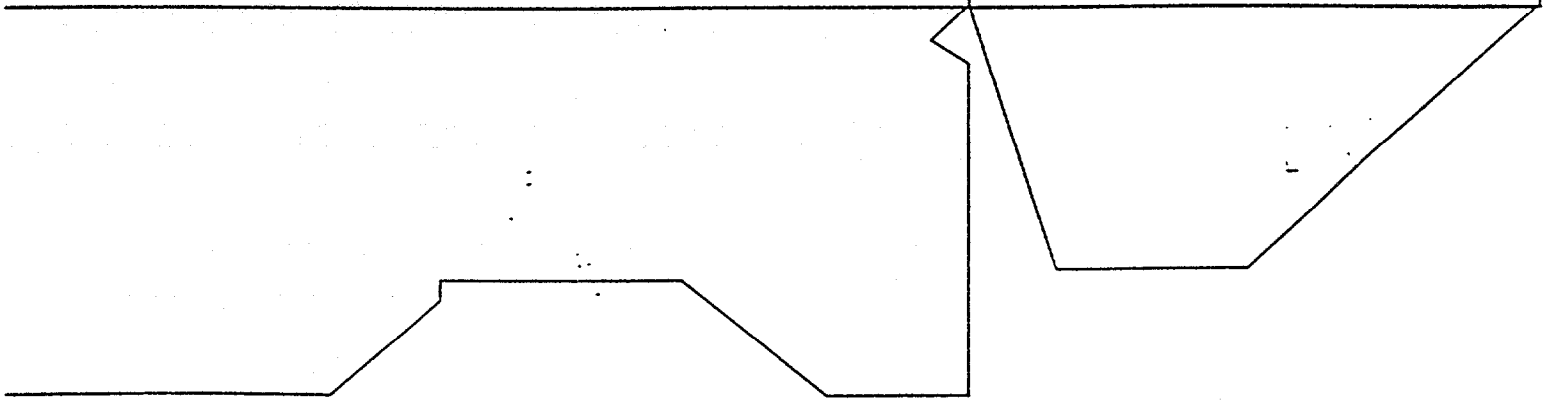
Hoechst Roussel Vet, S.A.
Distributed by:
Hoechst Roussel Vet
30 Independence Blvd.
Warren, NJ 07059



Revalor-200

(trenbolone acetate and estradiol)

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

Box of 10 x 10 Cartridge Implants

Manufactured by a non-sterilizing process

Hoechst Roussel Vet

0 21784 82000 4

PACKAGE QUANTITIES:
Box of 10 x 10 implants
Contains 100 doses in ten cartridges with ten implants per cartridge, each dose contains 10 small yellow pellets. Each pellet contains 20 mg of trenbolone and 2 mg estradiol.

STORAGE CONDITIONS:
Store in a refrigerator (2-8° C; 36-47° F) and protect from sunlight. Use before the expiration date printed on the box and on the cartridge.

USES:
This product is a slow-release anabolic agent containing trenbolone acetate and estradiol which increases rate of weight gain and improves feed efficiency in feedlot steers.

NOTE:
Studies have demonstrated that the administration of Revalor®-200 can result in decreased marbling scores when compared to non-implanted steers.

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0 21784 82000 4

Revalor-200

(trenbolone acetate and estradiol)

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

NET CONTENTS

Box of 10 x 100 dose packages

Manufactured by a non-sterilizing process

STORAGE CONDITIONS:

Store in a refrigerator (2-8° C; 36-47° F) and protect from sunlight. Use before the expiration date printed below and on the cartridge.

WARNING:

Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for Use in Humans. Implant pellets in the ear only. Any other location is in violation of Federal Law. Do not attempt salvage of implanted site for human or animal food.

482030-A

Hoechst Roussel Vet

Made in France by:
Hoechst Roussel Vet S.A.
Distributed by:
Hoechst Roussel Vet
30 Independence Blvd.
Warren, NJ 07059

Expiration Date

Lot Number

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Revalor®-200

30 0 21784 82000 5

(trenbolone acetate and estradiol)

FOR STEERS FED IN CONFINEMENT FOR SLAUGHTER

NET CONTENTS
4 x 1000 dose packages
Manufactured by a non-sterilizing process

STORAGE CONDITIONS:
Store in a refrigerator (2-8° C; 36-47° F) and protect from sunlight. Use before the expiration date printed below and on the cartridge.

WARNING:
Not to be used in animals intended for subsequent breeding, or in dairy animals. For Animal Treatment Only. Not for Use in Humans. Implant pellets in the ear only. Any other location is in violation of Federal Law. Do not attempt salvage of implanted site for human or animal food.

782000-A

Hoechst Roussel Vet

Made in France by:
Hoechst Roussel Vet S.A.
Distributed by:
Hoechst Roussel Vet
30 Independence Blvd.
Warren, NJ 07059

Expiration Date

Lot Number

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